REMARKS

Claims 1-12, 14-28, and 55-56 are pending in the application. Claim 1 has been canceled without prejudice, claims 2-4, 7, 11, 24 and 26 have been amended, and new claims 60-64 have been added. Accordingly, upon entry of the present Amendment, claims 2-12, 14-28, 55-56, and 60-64 will be pending.

Claims 2 and 24 have been amended to specify the sequences of human DEC-205 (SEQ ID NO:6) and mouse DEC-205 (SEQ ID NO:3). Support for amended claims 2 and 24 can be found at least, for example, at pages 46-47 (paragraph 0142) and the Sequence Listing, wherein Applicants teach the protein sequences of human DEC-205 (SEQ ID NO:6) and murine DEC-205 (SEQ ID NO:3). Further support for claims 2 and 24 can be found at least, for example, in original claim 46 and at page 4 (paragraph 0012), page 13 (paragraph 0039), page 49 (paragraph 0049), page 44 (paragraph 0132) of the specification as originally filed, wherein Applicants describe dendritic cell maturation factors that can be employed in the presently claimed methods.

Claim 2 and 24 have been further amended to specify that the recited antibody is linked to least one preselected antigen and at least one dendritic cell maturation factor, each on at least one preselected site on the antibody. Support for this amendment can be found, at least, for example at page 5 (paragraph 16), page 5 (paragraph 17), page 6 (paragraph 19), pages 13-14 (paragraph 43); pages 14-15 (paragraph 46); pages 33-34 (paragraph 111).

New claim 60 is drawn to a method of promoting highly efficient antigen presentation in a mammal comprising administering to the mammal (A) a conjugate comprising a subunit vaccine (*i.e.*, a cell-free vaccine prepared from purified antigenic components of pathogenic microorganism) linked to an antibody which binds to a human DEC-205 protein comprising SEQ ID NO:6 or a mouse DEC-205 protein comprising SEQ ID NO:3, and (B) at least one dendritic cell maturation factor, wherein said administering results in highly efficient antigen presentation and persistent presentation of antigen in the context of MHC class I antigens, such that persistence of MHC class I: antigen complexes in said mammal results in induction of a long lasting T cell response specific for said antigen. Support for new claim 60 can be found at least, for example, at page 6 (paragraph 119), page 32 (paragraph 108), page 68 (paragraph 208), page 96 (paragraph 294), and original claim 11.

New dependent claim 61 specifies that the subunit vaccine is selected from the group consisting of a bacterium, a virus and a tumor antigen (*e.g.,* a tumor or pathogenic organisms for which long term immunity and protection from disease is desired). Support for new claim 60 can be found at least, for example, at page 16 (paragraph 48), pages 39-41, paragraphs 124-125.

New dependent claim 62 specifies that the virus is selected from the group consisting of HIV-1, HPV, EBV, HSV, influenza virus and SARS virus. Support for new claim 62 can be found at least, for example, at page 16 (paragraph 48), pages 39-41, paragraphs 124-125.

New dependent claim 63 specifies that the method results in priming of CD8+ T cells specific for the subunit vaccine. Support for new claim 63 can be found at least, for example, at page 6 (paragraph 19), page 98 (paragraph 297), and original claim 11.

New dependent claim 64 specifies that the dendritic cell maturation factor is selected from the group consisting of an anti-CD40 antibody, an inflammatory cytokine, poly I/C, single strand RNA, DNA, CpG, ligation of IL-1 receptor, ligation of TNF receptor, ligation of TOLL-like receptors, activation of TRAF-6, and activation of NF-κ, and wherein said administering results in highly efficient antigen presentation. Support for new claim 64 can be found, at least, for example at pages 46-47 (paragraph 0142), page 4 (paragraph 0012), page 6 (paragraph 19), page 13 (paragraph 0039), page 32 (paragraph 108), page 49 (paragraph 0049), page 44 (paragraph 0132), page 68 (paragraph 208), page 96 (paragraph 294), original claim 11, page 111 (Abstract) and the Sequence Listing.

New dependent claim 65 specifies that the administration results in persistent presentation of antigen in the context of MHC class I antigens such that persistence of MHC class I: antigen complexes in said mammal results in induction of a long lasting T cell response specific for said antigen; and wherein such persistent presentation of antigen is analogous to a systemic infection as evidenced by presentation of antigen in most lymphoid tissue. Support for new claim 65 can be found, at least, for example at pages 7-8 (paragraph 21) and page 27 (paragraph 90).

No new matter has been added. The amendments presented herein should in no way be construed as an acquiescence to any of the Examiner's rejections and were made solely in the interest of expediting prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Information Disclosure Statements

Applicants submit herewith a Supplemental Information Disclosure Statement to make of record additional Office Actions which have issued in related cases previously made of record.

Rejection of Claims 1-12, 14-28, 46 and 55-56 Under 35 U.S.C. § 112

Claims 1-12, 14-28, 46 and 55-56 are rejected as failing to comply with the written description requirement. In particular, the Examiner asserts that the specification only provides the amino acid sequences encoding full length murine and full length human DEC-205 and does not provide adequate written description for methods which encompass an anti-DEC antibody which binds mutants/variants of murine DEC-205 or human DEC-205.

Applicants respectfully traverse this rejection. However, to expedite prosecution, Applicants have canceled claim 1, and amended claims 2 and 24 to specify the particular human and mouse DEC-205 sequences disclosed in the specification, thereby obviating this rejection. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejection of Claims 1-12, 14-28, 46 and 55-56 Under 35 U.S.C. § 112

Claims 1-12, 14-28, 46 and 55-56 are rejected as failing to comply with the written description requirement. In particular, the Examiner asserts that, while the specification provides several examples of dendritic cell maturation factors, it does not provide support for variants and mutants of dendritic cell maturation factors. Additionally, the Examiner is of the opinion that "the claims encompass a vast collection of unknown molecules with the functional activity recited in the claims wherein the identity of such molecules is unknown and structurally unpredictable (mimetics, nonprotein molecules, *etc*)."

Applicants respectfully traverse this rejection for the reasons previously made of record. Specifically, to meet the written description requirement of the first paragraph of 35 U.S.C. § 112, it is not necessary that a patent specification describe *each* and *every* specific member of a genus recited in a claim. "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. A 'representative number of species' means that the species which are adequately described

are representative of the entire genus." See MPEP § 2163.05 and *The Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997). In the present case, Applicants' specification describes numerous representative species of dendritic cell maturation factors to support the genus of dendritic cell maturation factors that is encompassed by the presently claimed methods (see, for example, page 13, paragraph 39 of the specification as originally filed). For example, the presently claimed methods can encompass dendritic cell maturation factors, such as an anti-CD40 antibody, an inflammatory cytokine, poly I/C, single strand RNA, DNA, CpG, ligation of IL-1 receptor, ligation of TNF receptor, ligation of TOLL-like receptors, and activation of TRAF-6, and activation of NF-κ.

Moreover, importantly, it is firmly established that a patent specification need not describe information that was well known in the art to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Indeed, the written description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. In *Capon v. Eshhar,* 418 F.3d 1349, 1357 (Fed. Cir. 2005) (hereinafter "*Capon*"), the Federal Circuit explained that "[p]recedent illustrates that the determination of what is needed to support generic claims to biological subject matter depends on a *variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter*. Id. at 1359 (emphasis added)." Accordingly, if the art is mature, less written description is required.

Specifically, in *Capon*, the claims at issue were drawn to DNA molecules encoding chimeric cell-surface receptor proteins made up of two portions having art-recognized (known) amino acid and nucleotide sequences. The Federal Circuit vacated the Board of Patent Appeals and Interference's decision invalidating these claims for lack of written description on the grounds that the sequences of the claimed chimeric DNA molecules were not explicitly disclosed in specification. The Federal Circuit held that the written description requirement did not require recitation of the nucleotide sequence of the claimed DNA in the specification because the sequence was already known in the field.

The facts of *Capon* parallel those of the present application. Similar to *Capon*, Applicants should not be required to describe each and every dendritic cell maturation factor in the specification, since such factors were clearly well known in the art at the time of filing

the present application. For example, as evidenced by column 4, paragraph 1, of U.S. Patent No.: 6,602,709 (filed February 19, 1999; enclosed herewith as Appendix A), Reddy *et al.*, (*Blood.* 1997 Nov 1;90(9):3640-6; enclosed herewith as Appendix B), and Cella *et al.*, (*Curr. Opin. Immunol.* 1997;9(1):396–404; enclosed herewith as Appendix C), numerous dendritic cell maturation factors were known in the art prior to the present invention.

Accordingly, in view of the numerous representative species described in Applicant's specification and, importantly, the fact that dendritic cell maturation factors were well known in the art at the time of filing, the present application provides more than adequate written description for the claimed genus of dendritic cell maturation factors encompassed by the presently claimed methods. Accordingly, the requirement of 35 U.S.C. § 112, first paragraph for written description has been satisfied and Applicants respectfully request reconsideration and withdrawal of this rejection.

Priority and Rejection of Claims 1, 3-7, 10-11, 14-17, 19, 21-25, 46 and 55 Under 35 U.S.C. § 102(b)

The Examiner asserts that the pending claims are anticipated by Bonifaz *et al.*, (*J Exp Med.*, 196(12):1627-38 (2002 Dec 16)) under 35 U.S.C. § 102(b). The Examiner relies on Bonifaz *et al.* for teaching *in vivo* subcutaneous administration to a mammal of a non-replicating antigen/anti-DEC-205 monoclonal antibody covalent conjugate and a dendritic cell maturation factor (agonist anti-CD40 antibody), wherein the dendritic cells are contacted with the aforementioned reagents *in vivo*.

Applicants respectfully traverse this rejection. Claims 2 and 24 are drawn to methods which encompass administering an antibody which binds to a human DEC-205 protein comprising SEQ ID NO:6 or a mouse DEC-205 protein comprising SEQ ID NO:3, ***wherein the antibody is linked to least one preselected antigen and at least one dendritic cell maturation factor, each on at least one preselected site on the antibody***. In other words, these claims encompass a hybrid molecule comprising three components: an anti-DEC 205 antibody, an antigen, and a dendritic cell maturation factor. As described in the specification at page 16 (lines 13-23), this recombinant molecule eliminates the need for separate administration of dendritic cell maturation factor. Specifically, the specification teaches that:

> Alternatively, rather than administering the dendritic cell maturation factor separately, the recombinant vaccine composition may also contain a third

> vector containing a gene encoding a dendritic cell maturation factor, operatively associated with a promoter capable of directing expression of the gene in the mammal. The expression of the antigen, the antibody and the dendritic cell maturation factor may be under the control of individual promoters or under the control of one promoter. Thus, upon delivery to a subject in which immunity to a specific pathogen is desired, ***the recombinant vaccine will encompass the antigen, the antibody for enhancing delivery to a dendritic cell having a specific receptor for DEC-205 on its surface, as well as the dendritic cell maturation factor*** necessary for increasing maturation of the cell and for enhanced antigen presentation and subsequent induction of highly efficient and long lasting immune responses, particular T cell responses.

Moreover, amended claims 5 and 24 and new claim 65 specify that administration results in ***persistent presentation of antigen***. Specifically, as described, for example, in the specification at page 6 (paragraph 18), page 7 (paragraph 20), page 9 (paragraph 27), pages 26-27 (paragraph 88), page 65 (paragraph 194) Applicants were the first to discover a means for inducing persistent antigen presentation, which results in a ***robust and long lasting immune response***. For example, the methods result in the predetermined antigen being significantly more effective in inducing a robust and ***long-lasting T cell response*** and in expanding antigen-specific CD4+ and CD8+ T cells in the mammal, as compared to an antigen administered without conjugation to anti-DEC-205 antibody fragments and delivered without combining the antigen with a dendritic cell maturation factor.

Additionally, new claim 60 specifies administration of a conjugate comprising a ***subunit vaccine*** (*i.e.*, a cell-free vaccine prepared from purified antigenic components of pathogenic microorganism) linked to an antibody which binds to a human DEC-205 protein comprising SEQ ID NO:6 or a mouse DEC-205 protein comprising SEQ ID NO:3, and at least one dendritic cell maturation factor, wherein said administering results in highly efficient and ***persistent presentation of antigen***.

For a prior art reference to anticipate, in terms of 35 U.S.C. § 102, a claimed invention, the prior art must teach each and every element of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Contrary to the Examiner's assertion, Bonifaz *et al.* do not teach an antibody which binds to a human DEC-205 protein comprising SEQ ID NO:6 or a mouse DEC-205 protein comprising SEQ ID NO:3, ***wherein the antibody is linked to least one preselected antigen and at least one dendritic cell maturation factor, each on at least one preselected site on the antibody***. Nor

do Bonifaz *et al.* teach ***persistent presentation of antigen***, which results in a ***robust and long lasting immune response***. Nor do Bonifaz *et al.* teach the induction of highly efficient and ***persistent antigen presentation*** with ***subunit vaccines***. Instead, Bonifaz *et al.* teach ovalbumin protein (OVA) chemically coupled to αDEC-205 antibody administered in conjunction with a dendritic cell maturation stimulus.

Accordingly, since Bonifaz *et al.* fail to teach or suggest each and every element of the pending claims, Applicants respectfully request that this section 102(b) rejection be reconsidered and withdrawn.

Rejction of Claims 1, 3-12, 14-28 and 55-56 Under 35 U.S.C. § 103(a)

Claims 1, 3-12, 14-28, 46 and 55-56 are rejected under 35 U.S.C. § 103(a) as being obvious over Bonifaz *et al.* in view of Germeraad *et al.* (US 2005/0037001). The Examiner relies on Bonifaz *et al.* for the reasons discussed above. The Examiner relies on Germeraad *et al.* for teaching that in vivo administration of conjugates of a humanized antibody against a dendritic cell molecule and a tumor antigen can be used to generate an immune response to said antigen.

Applicants respectfully traverse this rejection. As discussed above, Bonifaz *et al.* do not teach an antibody which binds to a human DEC-205 protein comprising SEQ ID NO:6 or a mouse DEC-205 protein comprising SEQ ID NO:3, ***wherein the antibody is linked to least one preselected antigen and at least one dendritic cell maturation factor, each on at least one preselected site on the antibody***. Nor do Bonifaz *et al.* teach ***persistent presentation of antigen***, which results in a ***robust and long lasting immune response***. Nor do Bonifaz *et al.* teach the induction of highly efficient and ***persistent antigen presentation*** with ***subunit vaccines***.

Indeed, prior to the present invention, the prior art had failed to achieve robust, long lasting T cell responses with subunit vaccines (*e.g.*, antigenic components of pathogenic organisms). Specifically, as described in the specification at page 65 (paragraph 194):

> It has been difficult up to the time of the present invention to be able to achieve such results, especially with T cell responses, wherein it has generally been observed that only live attenuated vaccines could achieve such dramatic T cell responses. It has generally been known that such robust T cell responses could not be achieved with non-replicating vaccines, thus there has always been a need for delivery of the non-replicating vaccine in an adjuvant, in addition for the need for several booster injections. This is not the case using

> the methods of the present invention. Accordingly, the methods of the present invention provide for a novel strategy for delivery of any microbial or tumor cell antigen to a subject such that a single injection may be sufficient to provide for highly efficient antigen presentation and subsequent immunity.

Moreover, as described at page 35 (paragraph 114):

> Unexpectedly, the inventors have found that a single low subcutaneous dose of a protein-based vaccine was able to charge DCs with antigen systemically and for long periods, particularly on MHC class I products. In parallel, the mice developed immunity, including $CD8^+$ T cell mediated immunity, which was considerably enhanced relative to prior methods of immunization with 1000 fold higher doses of antigen and was associated with stronger protection in anti-viral and anti-tumor models. More importantly, the inventors have identified a means of generating long lasting cellular immunity against non-replicating antigens, and have thus provided methods of generating T cell responses that mimic those seen in individuals that have experienced an active infection.

Further, as exemplified in the specification at pages 100-101 (paragraphs 304-305) "a single intracutaneous dose of only 50 ng of DC-targeted antigen is effective in generating protective immunity" in a murine model of vaccinia virus infection. Accordingly, Applicants were the first to discover methods for inducing ***persistent presentation of antigen***, which result in a ***robust and long lasting immune response***, particularly with ***subunit vaccines***. As discussed above, Bonifaz *et al.* fail to teach or suggest such methods, as claimed.

The secondary reference (Germeraad *et al.*) fails to cure this deficiency. Specifically, Germeraad *et al.* simply teaches conjugates for targeting antigen-presenting cells comprising at least one antigenic moiety conjugated to a targeting moiety that is capable of binding to a cell surface structure of an antigen-presenting cell. Germeraad *et al.* do <u>not</u> teach an antibody which binds to a human DEC-205 protein comprising SEQ ID NO:6 or a mouse DEC-205 protein comprising SEQ ID NO:3, ***wherein the antibody is linked to least one preselected antigen and at least one dendritic cell maturation factor, each on at least one preselected site on the antibody***. Nor do Germeraad *et al.* teach ***persistent presentation of antigen***, which results in a ***robust and long lasting immune response***, let alone using a ***subunit vaccine***. Therefore, even if one of ordinary skill had combined the cited references, they would not have arrived at the claimed methods. As such, the Examiner has failed to establish even a prima facie case of obviousness for the presently claimed methods.

Rejection of Claim 2 Under 35 U.S.C. § 103(a)

Claims 2 is rejected under 35 U.S.C. § 103(a) as being obvious over Bonifaz *et al.* in view of Germeraad *et al.* (US 2005/0037001) and Lasky *et. al.* (US 6,117,977). The Examiner relies on Bonifaz *et al.* and Germeraad *et al.* for the reasons discussed above. The Examiner relies on Lasky *et al.* for teaching bispecific conjugates wherein one arm of the conjugate recognizes a type C lectin, such as DEC-205.

Applicants respectfully traverse this rejection. Bonifaz *et al.* do not teach or suggest an antibody which binds to a human DEC-205 protein comprising SEQ ID NO:6 or a mouse DEC-205 protein comprising SEQ ID NO:3, ***wherein the antibody is linked to least one preselected antigen and at least one dendritic cell maturation factor, each on at least one preselected site on the antibody***. Nor do Bonifaz *et al.* teach ***persistent presentation of antigen***, which results in a ***robust and long lasting immune response***, let alone using a ***subunit vaccine***. In fact, as discussed in detail above, the prior art had failed to achieve robust, long lasting T cell responses from subunit vaccines (*e.g.*, antigenic components of pathogenic organisms).

The secondary references of Germeraad *et al.* and Lasky *et al.* fail to cure these deficiencies. Specifically, Germeraad *et al.* simply teach conjugates for targeting antigen-presenting cells comprising at least one antigenic moiety conjugated to a targeting moiety that is capable of binding to a cell surface structure of an antigen-presenting cell. Lasky *et al.* merely teach bispecific antibodies, wherien one of the binding specificities is for a type C lectin and the other one is for any other antigen (*e.g.*, another member of the endocytic type C lectin family, or a selectin, such as, E-, L- or P-selectin). Accordingly, even if one of ordinary skill had combined the cited references, they would not have arrived at the claimed methods. As such, the Examiner has failed to establish even a prima facie case of obviousness for the presently claimed methods.

CONCLUSION

In view of the above amendments and remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney could be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 574-4700.

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Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY &
SCARBOROUGH, LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 573-4700
(617) 742-4214 (Fax)
Attorney/Agent For Applicants